REMARKS

Claims 17-22 and 26-29 are pending.

Claims 17-22 and 26-28 have been amended.

Claim 29 has been canceled.

Claims 1-16 and 23-25 are withdrawn.

Claims 17-21 are rejected under 35 U.S.C. § 112, first paragraph.

Claims 22 and 26 are rejected under 35 U.S.C. § 102 as being anticipated by Kendall et al. (1993).

Claims 22 and 27-29 are rejected under 35 U.S.C. § 103 as being unpatentable over Kendall et al. (1993) in view of Bujard et al. (1998).

I. REJECTION OF CLAIMS UNDER 35 U.S.C. §112, FIRST PARAGRAPH.

Claims 17-21 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is the Examiner's position that the specification while being enabling for a method of inhibiting neovascularization in the eye, comprising the intraocular co-administration of an AAV-vector which directs the expression of anti-angiogenic factors (i.e. VEGF and Flt-1), does not reasonably provide enablement for method of inhibiting neovascular disease of the eye comprising intraocular delivery of genes which direct the expression of an anti-angiogenic factor such that the disease is inhibited. The crux of the Examiner's argument is that because Applicants use a rat model which does not exhibit the disease, co-administration of anti-angiogenic factors cannot be shown to affirmatively rescue or ameliorate the disease. That is, according to the Examiner, the rat model used in the present invention is not an efficacious model of neovascular ocular disease because the animal does not develop the disease, and therefore amelioration of such disease cannot be proven.

As detailed below, Applicants have amended claim 17, and to the extent that these rejections are not obviated by the amended claim, they are respectfully traversed.

As amended, an aspect of the claimed invention recites methods of inhibiting angiogenic factors of neovascular diseases in the eye (p.22 of specification, line 1). The specification further states that "[w]hile there are many animal models of *retinal* neovascularization ..., there are fewer models of choiroidal neovascularization... (emphasis added)." The present invention simulates subretinal and choroidal neovascularization by: (1) injection of angiogenic transgene (p.23, lines 1-5); (2) optic nerve (ON) crush (p.24, lines 24); (3) increase in intraocular pressure (p.25, lines 1-2).

The claimed invention simulates subretinal and choiroidal neovascularization by either introduction of angiogenic transgenes or by inducing tissue damage, which stimulates angiogenic factors in the recovering tissue. Lip et al. (2002) describe that levels of VEGF (a naturally occurring protein that ischemic tissues secrete and when introduced to endothelial cells stimulates the development of new blood vessels, or

angiogenesis), "were elevated in patients with normal tension glaucoma and primary open angle glaucoma (Abstract)." Lip et al., "Plasma vascular endothelial growth factor, soluble VEGT receptor FLT-1, and von Willebrand factor in glaucoma," *Br. J. Ophthalmol*, 86(11): 1299-302 (2002). Thus, retinal tissue damage stimulates angiogenic factors as shown by increased levels of VEGF, an angiogenic factor.

Moreover, Lip et al., (2002) showed that soluble FLT-1 (sFLT-1) levels were significantly lower in patients with normal tension glaucoma and primary open angle glaucoma when compared to healthy controls (Abstract)." Lip et al., *supra*. Soluble FLT-1 is a fms-like tyrosine kinase 1 receptor that is a membrane-bound receptor of VEGF (VEGF Receptor 1). It has been shown that a sFLT-1 has angiostatic or anti-angiogenesis properties, probably by way of its antagonist activity against VEGF by binding to VEGF and possibly by binding and blocking the external domain of the membrane-bound FLT-1. Kendall et al. "Specificity of vascular endothelial cell growth factor receptor ligand binding domains," *Biochem. Biophys. Res. Commun.* 201(1):326-30 (1994).

Hence, damage to the optic nerve by optic nerve crush or increase in intraocular pressure as performed in the present invention, inhibiting angiogenesis or neovascularization by co-administration of AAV-vectors which express anti-angiogenic factors, is a good model to show inhibition of neovascularization. Therefore, the specification does describe the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Further, the Examiner cites Romano et al. (1999) which raise issues regarding gene therapy efficacy and Ali et al. (1997) which raises issues regarding adeno-associated viral vectors. With regards to issues raised by Romano et al. (1999), the claimed invention is supported by the specification - that co-administration of anti-angiogenic factors to a damaged eye, which models the diseased state, inhibits angiogenesis as shown by histological data (see Example 5, Example 6, part C, subpart 2 and 3; Example 9, part B and C; Examples 15, 16 and17). Therefore, the specification enables one skilled in the art to administer AAV-vectors to tissue damaged regions of the eye resulting in inhibition of neovascularization. Note, that the claimed

invention recites that the claimed method inhibits neovascularization. The claimed invention does not claim to cure or prevent the disease.

With regards to the Ali et al. (1997) reference, Ali et al. address issues when using adeno-associated viral vectors including lack of high titers and contamination of wild-type AV. These problems are addressed in the present invention in Example 1. First, to achieve high titer the present invention performs triple transfection protocols (p.31-32). The Western blot in FIG. 4 shows that the titer is sufficiently high that levels of protein are detectable. The issue of wild-type contamination is also addressed and the rAAV preparations contained less than 1 wild type AAV genome per 10^9 rAAV genomes (p.33, lines 1-2). Thus, neither high titer nor wild type AV contamination is an issue in the present invention.

Accordingly, the Examiner is respectfully requested to withdraw these rejections.

II. REJECTION OF CLAIMS UNDER 35 U.S.C. § 102.

Claims 22 and 26 are rejected under 35 U.S.C. §§ 102(a) and (e) as being anticipated by Kendall et al. (1993).

A. Summary of the prior art.

1. Kendall et al. (1993)

Kendall et al. teach cloning of sFLT-1 into the pGEM3Z vector.

Kendall et al. do not teach cloning of sFLT-1 into a retroviral gene delivery vector as in the claimed invention.

B. The claimed invention is not anticipated by Kendall et al. (1993)

As detailed below, Applicants have amended claims 22 and 26, and to the extent that this rejection is not obviated by this amendment, they are respectfully traversed because Kendall et al. does not anticipate the claimed invention.

Also, in considering rejections based on anticipation under 35 U.S.C. §102, "[a]nticipation is established only when a single prior art reference discloses expressly or under the principles of inherency, each and every element of the claimed invention." RCA Corp. v. Applied Digital Data Systems, Inc., (1984 CAFC) 221 U.S.P.Q. 385. The stand for lack of novelty, that is, for "anticipation," is one of strict identity. To anticipate a claim, a patent or a single prior art reference must contain all of the essential elements of the particular claims. Schroeder v. Owens-Corning Fiberglass Corp., 514 F. 2d 901, 185 U.S. P.Q. 723 (9th Cir. 1975); and Cool-Fin Elecs. Corp. v. International Elec. Research Group, 491 F.2d 660, 180 U.S.P.Q. 481 (9th Cir. 1974).

Kendall et al. do not teach each and every element of the claimed invention, because Kendall et al. do not teach cloning of sFLT-1 into a retroviral gene delivery vector. Kendall et al. teach cloning of sFLT-1 into a plasmid vector which contains the origin of replication of the filamentous phage f1 (Promega). PGEM plasmid vectors are standard cloning vectors that contain T7 and SP6 polymerase promoters flanking a multiple cloning region with the alpha-peptide coding region of beta-galactosidase. These vectors are typical for use in *in vitro* transcription protocols and for production of circular single stranded DNA (Promega).

In contrast, the claimed invention clones sFLT-1 into a retroviral gene delivery vector, recombinant adeno-associated virus (rAAV). Retrovirus gene delivery vectors are described on pages 13-16. Retroviral constructs are comprised of 5'LTR, a tRNA binding site, a packaging signal, one or more heterologous sequences, an origin of second strand synthesis, a 3'LTR and wherein the vector lacks a *gag/pol* or *env* coding sequences (p.14, lines 5-8). Adeno-associated retroviral vector constructs are also described in the specification (p.15, lines 1-6). Also, expression of the cloned gene is not driven by the T7 or SP6 promoter as in pGEM vectors, rather they are driven by viral promoters including CMV promoters, RSV promoters, SV40 promoters or MoMLV promoters (p.15, lines 19-20).

Thus, it cannot be said that the cloning of sFLT-1 into pGEM3Z as described by Kendall et al. anticipates the cloning of sFLT-1 into a retroviral gene delivery vector because the pGEM3Z vector and the retroviral vectors recited in the claimed invention serve different purposes. For example, whereas retroviral recombinant vectors are capable of being introduced or injected into mammalian tissue to treat or inhibit a specific condition, pGEM3Z recombinant vectors are not for that purpose.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. REJECTION OF CLAIMS UNDER 35 U.S.C. § 103.

Claims 22 and 27-29 are rejected under 35 U.S.C. § 103(a) over Kendall et al. in view of Bujard et al. (1998).

A. Kendall et al. in view of Bujard et al.

Kendall et al. teach cloning of sFLT-1 into the pGEM3Z vector and Bujard et al. teach construction of recombinant replication defective retroviruses or adeno-associated retroviruses. It is the Examiner's position that Kendall et al. in view of Bujard et al. provide for combined teachings of sFLT-1 into a retroviral vector and thereby make obvious the claimed invention.

Claims 22 and 27-28 have been amended, and to the extent that this rejection is not obviated by this amendment, they are respectfully traversed because Kendall et al. in view of Bujard et al. do not make obvious the claimed invention.

Claim 29 has been canceled; it is now incorporated into claim 27.

B. The claimed invention is not obvious over the prior art.

First, the MPEP § 2143 clearly establishes that in order for a *prima facie* case of obviousness rejection to success, three basic criteria must be met: **(1)** there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; **(2)** there must be a reasonable expectation of success; and **(3)** the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In the present invention, the combination of references by the Examiner fails primarily because the prior art references do not teach or suggest all the claimed limitations.

The claimed invention recites a retroviral gene delivery vector which directs the expression of a neurotrophic or anti-angiogenic factor (amended claim 22). The retroviral gene delivery vector is selected from a group consisting of adeno-associated retroviruses and alpha-viruses (amended claim 27). Further the retroviral gene delivery

vector can be either HIV or FIV (claim 28). As discussed above, all these claim limitations are not satisfied when the combination of prior art references are combined. At best, when one skilled in the art combines the references of Kendall et al. and Bujard et al., the result is a recombinant retroviral vector containing the heterologous sequence of sFLT-1. However, this recombinant retroviral vector does not inhibit neovascularization of the diseased eye (amended claim 22). The administration of a retroviral gene delivery vector expressing a neurotrophic or anti-angiogenic factor to inhibit neovascularization of the diseased eye is the claimed invention.

Thus, as stated in the MPEP § 2143, in order for a *prima facie* case of obviousness rejection to succeed, the aforementioned three basic criteria must be met. The three basic criteria have not been met, and therefore, there is no *prima facie* case of obviousness.

Accordingly, the Examiner is respectfully requested to withdraw these rejections.

IV. CONCLUSION

Claims 17-22 and 26-28 remain pending. Claims 17-22 and 26-28 have been amended to improve their form and without adding new matter or raising new issues.

The rejections based on 35 U.S.C. §§ 102 and 103 have also been addressed above. Briefly, the claimed invention is patentably distinct from any of the prior art, alone or in combination, and absent the three factors of a *prima facie* case of obviousness as stated by the MPEP § 2143, there is no case of obviousness rejection. Therefore, the prior art references do not anticipate nor do they make obvious the claimed invention.

Thus, the claimed invention is patentable, accordingly the Examiner is respectfully requested to withdraw all rejections.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-1329.

Respectfully submitted,

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